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Original Research

Dual trigger does not improve the results of in vitro fertilization cycles in POSEIDON group 3: A retrospective cohort study

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Abstract

Aim: The aim of this study is to find out how the combined use of a gonadotropin-releasing hormone agonist (GnRH-a) and human chorionic gonadotropin (hCG) affects the success of IVF in women younger than 35 with diminished ovarian reserve (POSEIDON 3).

Material and Methods: This retrospective study included a total of 386 cycles in which embryo transfer occurred: 105 in the dual trigger group and 281 in the r-hCG trigger group. The two groups were compared regarding patient demographics, IVF cycle characteristics, and pregnancy outcomes.

Results: Demographic characteristics were similar in both groups. When the r-hCG and dual-trigger groups' cycles were compared, the number of retrieved oocytes, the number of metaphase II oocytes, the rates of fertilization and implantation, the number of embryos transferred, and the number of embryos frozen were all the same. When comparing the cycle characteristics of the r-hCG and dual-trigger groups, the retrieved oocytes, metaphase II oocytes, fertilization rates, implantation rates, number of embryos transferred, and number of cryopreserved embryos were similar. The implantation (46.6% vs. 47.6%, p=0.855), biochemical miscarriage (4.6% vs. 4.8%, 0.955), clinical miscarriage (7.8% vs. 6.7%, p=0.700), and ongoing pregnancy (34.2% vs. 36.2%, p=0.710) rates were similar. There were no statistically significant differences between the two groups.

Discussion: This study compared dual trigger and r-hCG trigger in women under 35 with diminished ovarian reserve for IVF outcomes. While some research suggested dual trigger benefits, this study found no significant differences in IVF cycle results or pregnancy outcomes between the groups. The limitations of the study include its retrospective design and small sample size. Further well-designed research is needed to recommend routine dual trigger usage for such patients.

Keywords

Dual Trigger, hCG Trigger, Diminished Ovarian Reserve, Pregnancy Outcomes

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Introduction

In IVF treatments, the objective of ovarian stimulation is to stimulate the existing follicles of infertile women to produce an acceptable number of mature eggs and embryos. In cycles with a higher number of mature oocytes, the cumulative live birth rate was found to be higher, according to a study with a large sample size [1]. Oocyte maturation occurs during the mid-cycle luteinizing hormone (LH) surge and minor follicle-stimulating hormone (FSH) surge in the natural cycle. Human chorionic gonadotropin is recommended as a trigger for retrieving mature oocytes from stimulated ovaries during IVF cycles because of its molecular and biological similarities to LH [2]. Using recombinant human chorionic gonadotropin (r-hCG) with a long half-life for oocyte maturation in individuals who are hyper responders may result in ovarian hyperstimulation syndrome (OHSS). GnRH agonists are indicated as the trigger in such situations because of their short half-lives. Since the agonist trigger promotes both LH and FSH secretion as in a normal cycle, studies suggest a higher number of mature oocytes when the gonadotrophin-releasing hormone agonist (GnRH-a) trigger is used as opposed to the hCG trigger. Despite this, a number of studies indicate that the use of GnRH agonist therapy alone to stimulate ovulation is linked to low pregnancy rates and substantial risks of early pregnancy loss owing to luteal phase failure [3,4]. Consequently, a dual trigger strategy with low-dose r-hCG was initially recommended [5]. Griffin et al. demonstrated that in cases of poor mature oocyte retrieval with r-hCG triggering, the mature oocytes considerably increased in the subsequent cycle when dual triggering was used [6]. Several studies indicated that dual triggering increases the total number of collected eggs and MII eggs, in addition to the implantation rate, clinical pregnancy rate, and live birth rate [5,7]. IVF therapy is difficult to manage in cases with diminished ovarian reserve (DOR) because they have a low number and quality of eggs [8]. 10–34% of all couples treated in IVF facilities are predicted to have DOR [9]. Several protocols have been proposed to increase the efficacy of ART in this patient population, and only a few have been shown to be successful [10]. Because of their diminished ovarian reserves, these patients may require multiple IVF cycles. This may result in physical, psychological, and financial difficulties for couples.

The purpose of this study was to determine whether dual triggering improves IVF pregnancy outcomes compared to r-hCG triggering in women under the age of 35 years with a diminished ovarian reserve, designated as POSEIDON Group 3 (Patient-Oriented Strategies Encompassing Individualized Oocyte Number) [11].

Primary and Secondary Outcomes

The primary outcome of the study was the ongoing pregnancy rate. Secondary outcomes were

fertilization, blastocyst development rate, and miscarriage rates.

Material and Methods

Patients who visited the Istanbul Medipol Mega Hospital IVF Center between 2013 and 2021 were included in this study. First, this was a retrospective study. The Ethical Committee of Medipol University approved the study protocol on 27-12-2021 with the protocol number E-10840098-772.02-6688. “Informed consent” was also obtained from each participant.

Women who are under 35 years of age with diminished ovarian reserve, Anti-Müllerian hormone (AMH) ≤1.2 ng/ml, and Antral follicle count (AFC) ≤5 were found eligible for the study [11].

Women with hereditary or acquired uterine anomalies and untreated endocrinological problems were excluded. The subjects were divided into two groups according to the triggering method used to induce ovulation: the “r-hCG group” using r-hCG 6500 IU as the trigger and the “dual trigger group” using r-hCG 6500 IU and 0.2 mg triptorelin acetate as the trigger. The demographic characteristics of both groups were compared, including maternal age, duration of infertility, cause of infertility, AMH, number of previous IVF treatments, and body mass index (BMI). In addition, data on IVF cycles, including the total gonadotropin dose, number of embryos transferred, number of mature oocytes, mature oocyte ratio, number of fertilized oocytes, blastocyst development rate, endometrial thickness, fertilization rate, and number of cryopreserved embryos were evaluated. In addition, the pregnancy outcomes of the two groups were compared in terms of implantation, miscarriage, and ongoing pregnancy rates. All participants received the GnRH antagonist protocol. After the transvaginal ultrasound examination, ovarian induction was initiated on the second day of menstruation. The starting dose of gonadotropin was chosen according to age, AMH level, size and number of antral follicles, and body mass index. Recombinant FSH (Gonal-f (Merck Serono)) was administrated to stimulate the ovaries of each patient. Following the cycle protocol, a GnRH antagonist (Cetrotide; Merck Serono Biopharma) was added when the follicle reached 13 mm in size.

When the diameter of the precursor follicle reached 18-20 mm, it was triggered with 0.2 mg triptorelin acetate (Decapeptyl; Ferring) or r-hCG 6500 IU (Ovitrelle; Merck Serono Biopharma) to stimulate oocyte maturation. Oocytes were collected 36 h after triggering, under the supervision of transvaginal ultrasonography. After collection, oocytes were cultured for 2 hours until denudation of the cumulus-oocyte complexes. Oocyte maturity was assessed immediately before ICSI and metaphase phase II (MII), and the oocytes were identified by the presence of polar bodies. After oocyte retrieval, progesterone vaginal gel (Crinone® 8% vaginal progesterone gel (90 mg)) (Central Pharma [Contract Packaging] Ltd., Merck GmbH, Germany) was used for luteal support. After five days, embryo transfer was performed. Once pregnancy occurred, progesterone vaginal gel was continued twice daily until the 12th week of gestation.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) (IBM Corp., USA). Categorical data were reported as raw frequencies with corresponding percentages, while continuous variables were shown as means with standard deviations (SD). The student’s t-test was used to compare normally distributed continuous data. Categorical data have been compared using the chi-square analysis. The statistical significance criterion was set at $p< 0.05$. To assess if the variables significantly affected the rates of ongoing pregnancy, a logistic regression analysis was conducted.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

In total, 386 embryo transfers in fresh cycles were examined in this study (n = 281 in the r-hCG group and 105 in the dual-trigger group). The r-hCG group and dual trigger group did not significantly and statistically differ in terms of demographic variables, including AMH level, BMI, female age, length of infertility, number of prior IVF cycles, and etiology of infertility (Table 1). No significant differences were found between the dual-trigger group and the r-hCG group according to IVF cycle characteristics such as the number of mature eggs, rate of mature eggs, number of fertilized eggs, fertilization rate, blastocyst development rate, number of cryopreserved embryos, and number of transferrable embryos. Endometrial thickness was significantly greater in the dual trigger group.

Table 1. Demographics and Cycle Characteristics.

Demographic Characteristics	hCG trigger n=281	Dual trigger n=105	p-value
Female age (mean±SD)	32.24±3.55	32.85±3.45	0.134[1]
Body mass index (mean±SD)	26.14±4.86	25.49±4.36	0.353[1]
AMH level (mean±SD)	0.353[1]	0.55±0.31	0.353[1]
Number of previous IVF trials (mean±SD)	0.87±1.37	0.86±1.20	0.955[1]
Duration of infertility (mean±SD)	5.27±4.21	5.03±3.61	0.090[1]
Cause of infertility (%)			
Female factor (%)	21,6(60/277)	23(23/100)	0.052[1]
Male factor (%)	26.7(74/277)	23(23/100)	0.466[1]
Unexplained infertility	62.5(173/277)	52(52/100)	0.068[1]
Cycle Characteristics			
Total gonadotropin dosage (mean ±SD)	2400.14±1290.21	2385.91±1290.80	0.923[1]
E2 level on trigger day (mean ± SD)	880.44±884.50	843.72±432.66	0.689[1]
Number of mature oocytes (mean ± SD)	2.81±1.18	2.62±1.14	0.143[1]
Mature oocyte rate (mean ± SD)	0.83±0.21	0.85±0.38	0.663[1]
Number of fertilized oocytes (mean ±SD)	2.49±1.10	2.33±1.08	0.196[1]
Fertilization rate (mean ± SD)	0.91±0.23	0.91±0.20	0.973[1]
Number of cryopreserved embryos (mean ± SD)	0.37±0.78	0.42±0.90	0.746[1]
Endometrial thickness (mean ± SD)	9.51±1.83	10.08±1.67	0.006[1]
Number of transferred embryos (mean ± SD)	1.63±0.49	1.59±0.57	0.241[1]
Blastocyst development rate	0.23±089	0.45±1.19	0.120[1]

[1]Student's t-test. [2]Chi-square test

Table 2. Pregnancy outcomes per transfer cycle.

	hCG trigger	Dual trigger	P value
Biochemical miscarriage (%)	4.6 (13/281)	4.8 (5/105)	0.955[2]
Clinic miscarriage rate (%)	7.8 (22/281)	6.7 (7/105)	0.700[2]
Implantation rate (%)	46.6 (131/281)	47.6 (50/105)	0.855[2]
Ongoing pregnancy rate (%)	34.2 (96/281)	36.2 (38/105)	0.710[2]

[2]Chi-square test

Table 3. Logistic regression analysis.

	Coefficient	P-Value	Odds Ratio (95% CI)
Age	-0.138	0.049	0.871 (0.759 – 1.000)
BMI	0.033	0.569	1.033(0.924 – 1.155
Trigger method	0.142	0.754	1.152 (0.474 – 2.799)
AMH level	0.507	0.498	1.660 (0.384 – 7.184)
E2 level on trigger day	0.001	0.062	1.001 (1.000 – 1.002)
Total gonadotropin dosage	0.000	0.406	1.000(0.999 – 1.000)
Number of cryopreserved embryos	0.715	0.023	2.044(1.104 – 3.782)
Endometrial thickness	0.011	0.944	1.011(0.740 – 1.382)
Constant	0.527	0.879	1.695

Furthermore, the mean number of cryo-preservable embryos after fresh embryo transfer was not significantly different between the two groups (Table 2). In addition, pregnancy results in both groups were compared (implantation rate per transfer (46.6% vs. 47.6%), biochemical miscarriage rate per transfer (4.6 vs. 4.8%), clinical miscarriage rate per transfer (6.7 vs. 7%), and ongoing pregnancy rate per transfer (36.2% vs. 34.2%)) (Table 3). Multivariate logistic regression analysis was conducted. egression models included female age, AMH level, BMI, trigger method, estradiol level on trigger day, total gonadotropin dosage, and number of cryopreserved embryos. It was discovered that the trigger method was not associated with the ongoing pregnancy rate for each transfer cycle. The number of cryopreserved embryos and female age had a significant effect on ongoing pregnancy rates ($p< 0.05$). A one-unit increase in age decreased the probability of ongoing pregnancy by 0.8-fold. An increase in the number of cryopreserved embryos by one unit increased the probability of sustained pregnancy by 2.0-fold.

Discussion

This study evaluated whether dual triggering is superior to r-hCG triggering in women under 35 years of age with diminished ovarian reserve. There was no difference in the IVF cycle results and pregnancy outcomes after comparison.

Recent research has suggested the use of a dual-trigger technique to stimulate oocyte maturation in IVF patients. However, the design, methods, and outcomes of studies comparing the effectiveness of the dual trigger to that of the r-hCG trigger alone differ significantly. Multiple studies have suggested that the total number of collected eggs, mature eggs, and transferrable embryos is much greater when a dual trigger is used than when a conventional trigger is used with r-hCG alone. In the aforementioned studies, dual triggering was also correlated with increased implantation and clinical pregnancy rates [12,15]. In contrast to our research, these studies demonstrated that the dual trigger generated superior outcomes compared to the r-hCG trigger; nonetheless, their study groups were distinct from ours. Lin et al., for instance, evaluated older women with diminished ovarian reserve. In contrast to our study group, Haas et al. conducted their most recent randomized controlled trial on women with greater ovarian reserve, and no diminished ovarian reserve [13]. In contrast to our study group, Chern et al. have demonstrated

that the dual trigger improves IVF outcomes in patients aged 35 years and older with diminished ovarian reserve, also known as POSEIDON Group 4 [14]. In the 2016 review, Oliver et al. did not find any differences in the number of transferred or frozen embryos between the dual trigger and hCG groups for poor responders; however, the implantation rate of the dual trigger group was higher [15]. However, studies conducted parallel with ours did not report any differences in the pregnancy outcomes between the r-hCG and dual-trigger groups [16,19]. Herbemont et al. discovered that dual triggering enhanced the number of mature eggs in instances where fewer mature eggs than predicted had been gathered. Despite the increase in the number of mature oocytes in these cases, no differences were found in the fertilization and clinical pregnancy rates. In the dual trigger group, the number of mature oocytes was higher, but the fertilization, implantation, miscarriage, and clinical pregnancy rates were not statistically significant [17]. In a randomized, prospective, controlled study on normoresponder patients, the number of collected eggs and mature eggs was not different between the dual trigger and r-hCG trigger groups, however, the pregnancy rate of the r-hCG group was higher. In contrast, the number of embryos in the top-quality and frozen embryos was greater in the dual trigger group [20].

In our study, endometrial thickness was statistically significantly higher in the dual trigger group, but the pregnancy outcomes of both groups were similar. The blastocyst development rate was higher in the dual trigger group, although there was no statistical difference, and we believe that these findings should be evaluated in future randomized controlled studies.

Our study group differed from the groups in the literature when comparing the dual trigger and r-hCG groups. This study is the first to compare dual triggers with hCG triggers in the POSEIDON 3 group. In our study, the logistic regression analysis demonstrated that the trigger technique had no influence on the ongoing pregnancy, whereas female age and the number of cryopreserved embryos did. Our research indicates that routine usage of the dual trigger does not significantly improve IVF cycles or pregnancy rates. In addition, dual triggering has inconsistent outcomes in different patient populations. There is no solid evidence that dual triggering is advantageous for all patients undergoing IVF or ICSI. To encourage routine dual trigger usage in women with diminished ovarian reserves, significant, well-designed research is required.

Conclusion

In younger patients with diminished ovarian reserves, the rates of mature oocytes, fertilization, number of cryopreserved embryos, implantation rate, clinical pregnancy rate, and miscarriage rate did not differ significantly between the r-hCG and dual-trigger groups.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of interest

The authors declare no conflict of interest.

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